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10/551,658	06/22/2006	Michael Gotthardt	BB-156	4607

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EXAMINER	
HILL, KEVIN KAI	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,658	GOTTHARDT ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,15 and 17-36* is/are pending in the application.

4a) Of the above claim(s) *1-9,11,12 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15,17-26 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Applicant has elected without traverse the invention of Group II, claims 13-26 and 31-34, drawn to a method for producing an inducible site-directed transgenic cell or organism comprising a mutated allele of a gene and a rescue allele of said mutated gene.

Within Group II, Applicant has elected the following species:
i) wherein the alternative structural elements to the genetic construct encoding the rescue allele, is a recombination target site, as recited in claim 15, specifically a Lox site;
ii) wherein the alternative mechanisms by which the rescue allele inhibits the function of a non-mutated allele, as recited in claim 16, is direct inhibition;
iii) wherein the specific number of mutated alleles, as recited in claim 20, is one;
iv) wherein the specific number of rescue alleles, as recited in claim 20, is one;
v) wherein the alternative host cell types, as recited in claim 19, is a mammalian cell;
vi) wherein the alternative biological subjects, as recited in claim 25, is a mammalian tissue;
vii) wherein the alternative inactivation techniques, as recited in claims 23 and 33, is via site-directed recombination via Cre/Lox;
viii) wherein the alternative settings in which the method is practiced, as recited in claim 24, in vivo;
ix) wherein the alternative temporal and/or local phenotypes, as recited in claim 32, is an embryonic lethal phenotype; and
x) wherein the alternative mutagenesis techniques, as recited in claim 31, is random integration of foreign DNA.

Amendments

Applicant's response and amendments, filed February 1, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 10, 14 and 16, withdrawn Claims 1-9, 11-12 and 27-30, amended Claims 13, 17-18, 22-23, 26 and 30-31, and added new claims, Claims 35-36. Applicant's new claims have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group.

Claims 1-9, 11-12 and 27-30 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 13, 15, 17-26 and 31-36 are under consideration.

Priority

This application is a 371 of PCT/EP04/02216, filed March 4, 2004. Applicant's claim for the benefit of the prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority of EPO 03008470.1, filed April 11, 2003 under 35 U.S.C. 119(a)-(d). A certified copy has been filed in the instant application.

Accordingly, the effective priority date of the instant application is granted as April 11, 2003.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 1, 2008 response will be addressed to the extent that they apply to current rejection(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

1. **The prior rejection of Claims 13-18, 22-23 and 26 under 35 U.S.C. 112, second paragraph is withdrawn** in light of Applicant's amendments to the claims to clarify the claimed subject matter.

2. **Claims 13, 26 and 31 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to Claims 13 and 26, the claims are indefinite in the recitation of the term "suitable" (line 10, respectively). Furthermore, there is insufficient antecedent basis for this limitation in the claim. As discussed in the prior Office Action, The term "suitable" in claims 13 and 26 is a relative term which renders the claim indefinite. The term "suitable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "suitable" is a subjective term because suitability is not specifically defined in the art and is subject to change from one artisan to the next. The metes and bounds are relative

to the artisan's interpretation and not specifically defined in the art. Furthermore, the term "said suitable" indicates that a specific mutagenesis technique has been previously recited in the claims. However, no such specific mutagenesis technique is previously recited.

With respect to Claim 31, the claim recites dependency upon Claim 14. However, Claim 14 has been cancelled. For the purposes of compact prosecution, the Examiner interprets Claim 31 to be dependent upon Claim 13.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. **Claims 13, 20-22, 24 and 26 stand rejected under 35 U.S.C. 102(b)** as being anticipated by Roemer et al (WO 01/60975; *of record in IDS).

With respect to claims 13 and 26, Roemer et al disclose a method for creating a diploid mutant cell of an organism in which the dosage of a specific gene can be modulated. By this method of the invention, one allele of a target gene in a diploid cell of an organism is disrupted [a mutated allele] while the second allele is modified by having its promoter replaced by a regulated promoter of heterologous origin [a conditionally inactivated rescue allele] (pg 10, lines 1-5), referred to herein as the GRACE method, where the acronym is derived from the phrase Gene Replacement And Conditional Expression. Roemer et al disclose the mutagenesis technique may comprise gene inactivation by insertion or replacement of a nucleotide sequence (pg 5, lines 1-2), wherein the process may be repeated with each and every gene of the organism (substitution). Roemer et al teach the conditionally inducible rescue construct is able to restore those functions/activities rendered mutant by the mutated alleles (pg 7, lines 1-11).

With respect to claim 20, Roemer et al disclose the use of diploid organisms, wherein a first allele is rendered mutant and a second allele is rendered conditionally-inactivatable rescue allele.

With respect to claim 21, Roemer et al disclose the method useful for identifying genes required for growth, viability and survival (pg 5, lines 4-6; pg 83, lines 34-35).

With respect to claim 22, Roemer et al disclose the suitable inactivation technique via a tetracycline-regulatable promoter (pg 18, 5.2.2).

With respect to claim 24, Roemer et al disclose the method to be performed *in vivo*, as applied to yeast cells (pg 16, 5.2).

Applicant's Arguments

Applicant argues that the instant invention contrasts with Roemer et al in that the present invention uses a cell in which the wildtype allele, referred to in the subject application as the "rescue" allele can be conditionally inactivated. In other words, rather than turning on the expression of the wildtype gene (Roemer et al), the present invention switches off the expression of a wildtype gene in order to investigate the function of the mutated allele. The cited reference does not disclose the use of a rescue allele that can be conditionally inactivated.

Applicant's argument(s) has been fully considered, but is not persuasive. Roemer et al disclose that the rescue allele is under the control of a regulatable, heterologous promoter, Thus, Roemer et al disclose a method of producing an inducible site-directed mutant cell capable of conditional gene rescue, wherein the rescue allele is both "conditionally inactivated" as required by the claims, as well as "conditionally activated", depending upon the culture conditions to which the cells are exposed, e.g. the presence or absence of tetracycline.

4. **The prior rejection of Claims 13-17, 19-22, 24-26 and 34 under 35 U.S.C. 102(b)** as being anticipated by Shin et al (Nature 402:496-501, 1999) **is withdrawn** in light of Applicant's argument that Shin et al do not teach the mutagenesis technique does not lead to a disturbed interaction of the mutated gene product with other components of the cell because Shin et al are unable to detect mutant EdnrB mRNA encoded by the mutated allele.

5. **Claims 13, 17, 20-22, 24-26, 31 and 35-36 are rejected under 35 U.S.C. 102(b)** as being anticipated by Philip et al (J. Neurosci. 21(21):8417-8425, 2001).

This is a new rejection.

With respect to claims 13, 24 and 26, Philip et al teach a method for producing an inducible site-directed mutant cell and/or a non-human organism comprising a cell capable of conditional gene rescue, the method comprising introducing in a target cell a mutated allele of a gene to be mutated by using a mutagenesis technique, introducing in said target cell a rescue allele of said gene, wherein the rescue allele can be conditionally inactivated, wherein the mutagenesis technique comprises introducing a mutation wherein the exon or sub-exon level that leads to a disturbed interaction of the mutated gene product with other components of the cell, and generating a non-human mutant organism comprising said mutant cell. Philip et al teach the generation of transgenic flies comprising a first mutant allele comprising a transposon integration

resulting in weak and strong hypomorphic mutations (pg 456, Figure 1; pg 455, col. 2, Vol locus). Philip et al teach the conditional rescue of Vol mutants comprising a rescue allele under the control of a heat-shock promoter, wherein those of ordinary skill in the art recognize the heat-shock promoter can be conditionally activated and conditionally inactivated. The Vol mutants yield a mutant phenotype, and thus, absent evidence to the contrary, the mutation inherently leads to a disturbed interaction of the mutated gene product with at least one other component of the cell.

With respect to claims 17 and 25, Philip et al teach the Vol mutation yields a tissue-specific phenotype in that Vol-l transcripts are expressed selectively in the head; whereas, Vol-s transcripts are expressed in both head and body tissues (pg 455, Vol locus).

With respect to claims 20, 35 and 36, Philip et al teach the method to comprise the step of constructing flies comprising both the mutant allele and the rescue allele.

With respect to claim 21, the mutant allele affects both a temporal and local phenotype (pg 456-458).

With respect to claim 22, the rescue allele is conditionally inactivated by the inactivation technique of removing the flies from heat-shock temperatures.

With respect to claim 31, the mutagenesis technique employs random integration of foreign DNA.

6. **Claims 13, 15, 17, 19-26 and 32-36 are rejected under 35 U.S.C. 102(b)** as being anticipated by Gaussin et al (PNAS 99(5):2878-2883, 2002).

This is a new rejection.

With respect to claims 13, 19, 24-26 and 34, Gaussin et al teach a method for producing an inducible site-directed mutant cell and/or a non-human organism comprising a cell capable of conditional gene rescue, the method comprising introducing in a target cell a mutated allele of a gene to be mutated by using a mutagenesis technique, introducing in said target cell a rescue allele of said gene, wherein the rescue allele can be conditionally inactivated, wherein the mutagenesis technique comprises introducing a mutation wherein the exon or sub-exon level that leads to a disturbed interaction of the mutated gene product with other components of the cell, and generating a non-human mutant organism comprising said mutant cell. Gaussin et al teach

the mutation at the exon level, specifically deletion of exon 2 (pg 2879, Figure 1), that inherently leads to a disturbed interaction of the mutated gene product with at least one other component of the cell, absent evidence to the contrary, wherein the mutation causes an adverse phenotype (pg 2879, Figure 1; pg 2880, Figure 2) in a transgenic mouse.

With respect to claim 15, Gaussin et al teach the rescue allele comprises recombination target sites.

With respect to claims 17, 21 and 32, Gaussin et al teach the mutation yields a tissue-specific phenotype, specifically cardiac-restricted, or embryonic lethality.

With respect to claims 20, 35 and 36, Gaussin et al teach the method to comprise the step of constructing mice comprising both the mutant allele and the rescue allele.

With respect to claims 22-24 and 33, Gaussin et al teach the conditional inactivation of the rescue allele to be mediated via Cre/Lox recombination *in vivo*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **The prior rejection of Claims 13-22, 24-26, 32 and 34 are rejected under 35 U.S.C. 103(a)** as being obvious over Shin et al (Nature 402:496-501, 1999) and Gotthardt et al (J. Biol. Chem. 278(8): 6059-6065, 2003; available online December 2, 2002; *of record in IDS) **is withdrawn** in light of Applicant's argument regarding the teachings of Shin et al discussed above.

8. **Claims 13, 15, 17, 19-25 and 34 stand, and Claims 26, 31, 33 and 35-36 are newly rejected under 35 U.S.C. 103(a)** as being obvious over Roh et al (Mol. Endocrinol. 15(4): 600-613, 2001) and Tian et al (Developmental Biology 242:204-223, 2002).

This is a new rejection for the inclusion of Claims 26, 31 and 33, not annotated in the heading of the rejection in the prior Office Action.

Roh et al teach a method of making a transgenic mouse encoding a mutated allele of a gene, wherein said mutated allele comprises a mutation at the exon or sub-exon level, e.g. a deletion, such that the mutant allele encodes a truncated EGF receptor (pg 601, col. 1, ¶2), wherein the genetic construct comprising the mutated allele has integrated randomly into the host genomic DNA. The mutated allele is under the control of tetracycline-controlled transactivator (tTA), wherein expression of tTA is under the control of an exogenous promoter (pg 601, col. 1, ¶1), therefore the mutated allele is considered to be tissue-specific as per the tissue-specificity of the exogenous promoter regulating expression of tTA. The bi-transgenic mice (PRL-tTA/TetRE-EGFRtr) displayed adverse temporal and local phenotypes such as delayed eye opening and obvious dwarf phenotypes (pg 606, col. 2; pg 608, Figure 6).

Roh et al do not teach the transgenic mouse to further comprise a conditionally-inactivatable rescue allele, wherein the conditional inactivation is mediated by Cre/Lox site-specific recombination.

However, at the time of the invention, Tian et al taught a method of making a conditional rescue allele in mice, wherein the rescue allele is inactivated via Cre-mediated recombination that acts on Lox recognition target sites (Cre/Lox) to catalyze recombination between to (Lox) recognition sites to bring about modification of the associated DNA, specifically a deletion (pg 205, Figure 1). Because the Cre-mediated recombination event is under the control of an exogenous promoter-Cre transgene, e.g. a CAG-promoter (pg 208, col. 2), the rescue allele is considered to be subject to tissue-specific conditional regulation.

Tian et al teach steps of cultivating the target cell under conditions that allow for a selection of cells that contain both the mutated allele and the rescue allele of said gene (pgs 210-211, joining ¶, Generation of Allelic Series).

It would have been obvious to one of ordinary skill in the art to combine regulated mutated allele technology as taught by Roh et al with regulated rescue allele technology as taught by Tian et al with a reasonable chance of success because all the claimed elements [regulated mutated allele technology and regulated rescue allele technology] were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. It was well within the knowledge and skill of the ordinary artisan at the time of the invention to cross a first

transgenic mouse to second transgenic mouse to establish allelic series and assay genetic rescue or production of a mutant phenotype at different, desired stages of development. Such basic genetic strategies are employed by the ordinary artisan as a matter of course in the study of the artisan's gene of interest. The artisan need only cross a transgenic non-human organism, e.g. mouse, comprising a regulated mutated allele of the artisan's desired target gene to a transgenic non-human organism, e.g. mouse, comprising a regulated rescue allele of the artisan's desired target gene so as to combine both transgenes into the same transgenic non-human organism, wherein expression of the mutated allele and the rescue allele may each be regulated by known means coincidentally or sequentially, as per the needs of the artisan. Tian et al teach the genetic construct to be useful for generating allelic series of a desired gene, the motivation being that "early embryonic lethality resulting from complete loss-of-function mutations renders milder alleles valuable in the elucidation of roles at later developmental stages; consequently, this approach may provide an applicable method for extensive genetic analysis of genes of interest (Tian et al, pg 218, col. 1, first full ¶).

Thus, the invention as a whole is *prima facie* obvious.

9. **Claims 13, 18, 26 and 32 stand rejected under 35 U.S.C. 103(a)** as being obvious over Roh et al (Mol. Endocrinol. 15(4): 600-613, 2001) and Tian et al (Developmental Biology 242:204-223, 2002), as applied to claims 13-17, 19-26, 31 and 33-36 above, and in further view of Gotthardt et al (J. Biol. Chem. 278(8): 6059-6065, 2003; available online December 2, 2002; *of record in IDS).

Roh et al and Tian et al do not teach wherein the mutated and rescue alleles encode titin, or wherein the mutated allele causes an embryonic lethal phenotype. However, at the time of the invention, Gotthardt et al taught a method of making titin kinase domain-deficient mice that died as early embryos.

It would have been obvious to one of ordinary skill in the art to substitute the mutant and rescue alleles of Roh et al and Tian et al with the titin target gene as taught by Gotthardt et al with a reasonable chance of success because the simple substitution of one known, equivalent element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Roh et al and Tian et al taught how to make a mutated allele and a conditional rescue allele. Gotthardt et al taught that the titin locus is amenable to gene-targeted homologous recombination to create mutated alleles resulting in embryonic lethal effects. The ordinary artisan would need merely to transfer the technology taught by Roh et al and Tian et al and apply it to make the analogous mutated allele and rescue allele genetic constructs as applied to the titin locus of Gotthardt et al, wherein the mutated allele would be reasonably expected to yield the embryonic lethal phenotype in the absence of the conditional activation of the rescue allele.

Thus, the invention as a whole is *prima facie* obvious.

Applicant's Arguments

Applicant argues that the Examiner has used improper hindsight to reconstruct the prior art (Roh et al, Tian et al and Gogghardt et al) to arrive at the instant invention.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Tian et al teach the genetic construct to be useful for generating allelic series of a desired gene. Furthermore, "early embryonic lethality resulting from complete loss-of-function mutations renders milder alleles valuable in the elucidation of roles at later developmental stages; consequently, this approach may provide an applicable method for extensive genetic analysis of genes of interest (pg 218, col. 1, first full ¶), e.g. titin. It was well within the knowledge and skill of the ordinary artisan at the time of the invention to cross a first transgenic mouse to second transgenic mouse to establish allelic series and assay genetic rescue or production of a mutant phenotype at different, desired stages of development. Such basic genetic strategies are employed by the ordinary artisan as a matter of course in the study of the artisan's gene of interest.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633